A narrow view of optimal weight for health generates the obesity paradox$^{1,2}$

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The "obesity paradox" is represented by a range of observations that suggest a lower risk of mortality in individuals who have a weight (adjusted for height) in the overweight or class I obese range rather than in the normal weight range. Mortality curves for a given BMI for any population are generally U-shaped with increased mortality at both ends. There is debate as to where the nadir of mortality for BMI lies in the general adult community and the degree of increased risk, if any, that is associated with overweight or class I obesity when compared with the normal weight range (1, 2). The issues revolve around the selection of included studies, granularity of the BMI cutoffs selected, and how to adjust for potential bias associated with unintentional weight loss (reverse causation) and selective survival advantage (3). However, there are now a broad range of conditions in adults that are clearly associated with improved survival in overweight and class I obese adults. The article by Gonzalez et al (4) in this issue of the Journal provides another example of the obesity paradox, this time in patients with cancer who are commencing chemotherapy, and provides interesting insights into the importance of nutrition and body composition for survival.

The observational study, which follows 175 cancer patients, examined survival in relation to BMI classification and bioelectrical impedance analysis–derived estimates of fat-free mass (FFM) and fat mass (FM) to identify obesity and sarcopenia through an FM index and FFM index, respectively (5). The study has several author-acknowledged weaknesses, such as that body composition was measured by using bioelectrical impedance analysis, a methodology that needs to be validated in the population being studied and is highly dependent on the algorithm and assumptions being used (6). And we know nothing of the patients’ weight trajectories immediately before enrollment in the study. There was, however, clear evidence of an obesity paradox, with survival better in patients who were BMI-classified as overweight and obese at baseline. In addition, sarcopenia at baseline was problematic. Overweight and obesity as measured by BMI appeared to be associated with adequate FFM, because all individuals with sarcopenia were found in under- and normal-weight BMI categories. It is therefore clear that BMI was a strong predictor of survival and FFM is important, especially in those with a BMI (in kg/m²) < 25.

The so-called obesity paradox appears to have arisen through a flawed concept whereby the lowest mortality for adults lies in a single "normal BMI range" of 18.5–25 and that this range is not altered by age, sex, ethnicity, or state of health. The assumption that adults have an optimal weight range for health appears sound but that this weight range (corrected for height) is the same for all individuals under all conditions is biologically challenging, as this study shows. The state of health—in this case, cancer—has changed the context, and a higher weight, presumably associated with higher FM and FFM, is associated with a survival advantage. Given the serious consequences of cancer cachexia for those commencing chemotherapy, it appears that additional weight provides biological resilience and an advantage under these altered circumstances. We would argue therefore that this is not a paradox.

Obesity, a chronic condition, is strongly associated with an increased risk of cardiovascular disease, type 2 diabetes, and many cancers and reduces the quality and length of life (7). Yet, these 3 chronic disease consequences of obesity are included in the growing list of chronic conditions that show an upward shift in the BMI for mortality nadir (8). In addition, normal aging provides a similar alteration to the mortality-to-BMI relation, with people over the age of 70 y in the overweight or class I obese range having the lowest mortality (9). The concept of a flexible optimal weight that can be adapted to the individual’s age, ethnicity, and state of health is biologically plausible, perhaps logical, but presents us with public health and clinical dilemmas.

Intentional weight loss is broadly recommended for overweight and class I obese individuals, especially if they have a high risk of developing, or have developed, type 2 diabetes or cardiovascular disease, but we have no evidence of a mortality advantage. With established type 2 diabetes and cardiovascular disease alone, or in combination, there are a series of interventional and observational studies that have not found reductions in mortality or major cardiovascular events with weight loss. The Look AHEAD (Action for Health in Diabetes) Study found that an intensive diet and exercise program resulting in weight loss did not reduce cardiovascular events (10). Intentional weight loss using the medication sibutramine increased the risk of nonfatal cardiovascular events and did not alter overall mortality (11). A post hoc analysis of

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pioglitazone or placebo, as additions to patients’ concurrent diabetes medications, from a large randomized controlled trial showed an inverse association between baseline BMI and mortality. In addition, weight loss was associated with increased mortality, whereas weight gain was not (12). The only evidence that mortality is reduced with intentional weight loss comes from bariatric surgical studies in which the preintervention BMI is >35 (13).

Chronic diseases, malignancy, and aging are associated with reductions in lean body mass and especially muscle mass, lower bone mineral density, compromised nutrition, impaired physical function, and frailty. Overweight and class I obesity may provide biological resilience under these circumstances, with preservation of FFM one of several putative mechanisms. We need to better understand these mechanisms. Meanwhile, individualized lifestyle and behavioral programs with a focus on quality nutrition, physical activity, fitness, and maintaining function (ie, focusing more on the “environmental causes” of obesity than obesity per se) may be biologically preferable in overweight or class I obese people who are older or who suffer from malignancy or chronic disease, rather than trying to achieve a normal (for healthy younger adults) weight.

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